(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2005 (17.11.2005)

PCT

(10) International Publication Number
WO 2005/107760 A1

(51) International Patent Classification[7]: A61K 31/519, 31/4745, C07D 498/02, 491/02

(21) International Application Number: PCT/US2005/015118

(22) International Filing Date: 29 April 2005 (29.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/567,346 30 April 2004 (30.04.2004) US

(71) Applicant *(for all designated States except US)*: **IRM LLC** [US/US]; P.O. Box HM 2899, Hamilton, HM LX (BM).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HONG, Jiyong** [KR/US]; 3853 Ingraham Street #C206, San Diego, CA 92109 (US). **GRAY, Nathanael S.** [US/US]; 5652 Lamas Street, San Diego, CA 92122 (US). **SCHULTZ, Peter** [US/US]; 1650 La Jolla Rancho, La Jolla, CA 92037 (US).

(74) Agents: **REID, Scott, W.** et al.; The Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS AND COMPOSITIONS AS INDUCERS OF KERATINOCYTE DIFFERENTIATION

(57) Abstract: The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to induce undifferentiated keratinocytes to differentiate into terminally differentiated keratinocytes. The invention further provides compounds for the treatment of diseases or disorders associated with casein kinase II (CK2), TANK-binding kinase 1 (TBK1) and NIMA-related kinase 9 (NEK9).

WO 2005/107760 A1

COMPOUNDS AND COMPOSITIONS AS INDUCERS OF KERATINOCYTE DIFFERENTIATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Number 60/567,346, filed 30 April 2004. The full disclosure of this application is incorporated herein by reference in its entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to induce undifferentiated keratinocytes to differentiate into terminally differentiated keratinocytes. The invention further provides compounds for the treatment of diseases or disorders associated with casein kinase II, TANK-binding kinase 1 and NIMA-related kinase 9.

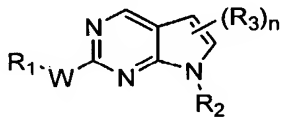
Background

[0003] The protein kinases represent a large family of proteins, which play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. A partial, non-limiting, list of these kinases include casein kinase II (CKII or CK-2), TANK-binding kinase 1 (TBK1) and NIMA-related kinase 9 (NEK9). Aberrant kinase activity has been observed in many disease states including benign and malignant proliferative disorders as well as diseases resulting from inappropriate activation of the immune and nervous systems.

[0004] The compounds of this invention modulate the activity of protein kinases and are, therefore, expected to be useful in the treatment of diseases associated with protein kinase activity. Further, the identification of small molecules that permit precise regulation of keratinocytes differentiation could inhibit or restore skin damage and facilitate therapeutic treatments of psoriasis and melanoma.

SUMMARY OF THE INVENTION

[0005] In one aspect, the present invention provides a method for inducing undifferentiated keratinocytes to differentiate into terminally differentiated keratinocytes, said method comprising contacting said undifferentiated keratinocytes with a compound of Formula I:



I

in which:

n is chosen from 0, 1 and 2; m is chosen from 0, 1, 2 and 3;

W is chosen from $-NR_4-$, $-S-$, $-O-$, $-S(O)-$ and $-S(O)_2-$; wherein R_4 is chosen from hydrogen and C_{1-6}alkyl;

R_1 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-XNR_5R_5$, $-XNR_5XNR_5R_5$, $-XNR_5XOR_5$, $-XOR_5$, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XC(O)NR_5R_5$, $-XOXR_6$ and $-XC(O)R_6$; wherein X is a bond or C_{1-6}alkylene; R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent of R_1 is further optionally substituted by 1 to 5 radicals independently chosen from C_{1-6}alkyl and C_{1-6}alkoxy;

R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-8}heteroarylC_{0-4}alkyl, $-XNR_5R_5$, $-XOR_5$, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XSNR_5R_5$, $-XS(O)NR_5R_5$, $-XS(O)_2NR_5R_5$, –

$XC(O)OR_5$, $-XOC(O)R_5$, $-XC(O)R_5$, $-XC(O)NR_5XNR_5R_5$, $-XC(O)NR_5R_5$, $-XC(O)NR_5XC(O)OR_5$, $-XC(O)NR_5XNR_5C(O)R_5$, $-XC(O)NR_5XNR_5C(O)OR_5$, $-XC(O)NR_5XOR_5$, $-XC(O)N(XOR_5)_2$, $-XNR_5C(O)R_5$, $-XC(O)NR_5R_6$, $-XC(O)R_6$, $-XR_7$, $-XR_6$ and $-XC(O)NR_5XR_7$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; and R_7 is cyano;

R_3 is chosen from halo, hydroxy, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XC(O)R_5$ and $-XC(O)OR_5$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

[0006] In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

[0007] In a third aspect, the present invention provides a method of treating a disease in an animal in which inhibition of kinase activity, particularly casein kinase II (CK2), TANK-binding kinase 1 (TBK1) and/or NIMA-related kinase 9 (NEK9) activity, can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0008] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which kinase activity, particularly casein kinase II (CK2), TANK-binding kinase 1 (TBK1) and/or NIMA-related kinase 9 (NEK9) activity, contributes to the pathology and/or symptomology of the disease.

[0009] In a fifth aspect, the present invention provides methods for screening for compounds that induce the differentiation of undifferentiated keratinocytes into differentiated keratinocytes.

[0010] In a sixth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0011] "Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be either straight-chained or branched. C_{1-4}-alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0012] "Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl may be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc.

[0013] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O) -, -S-, -S(O) - or -$S(O)_2$-, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, 1,1-dioxo-1l6-thiomorpholin-4-yl, etc.

[0014] "Halogen" (or halo) preferably represents chloro or fluoro, but may also be bromo or iodo.

[0015] "Involucrin" is a protein present in keratinocytes of epidermis and other stratified squamous epithelia. Involucrin first appears in the cell cytosol, but ultimately becomes cross-linked to membrane proteins by transglutaminase thus helping in the formation of an insoluble envelope beneath the plasma membrane.

[0016] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

[0017] The compounds of this invention can induce the differentiation of undifferentiated keratinocytes into differentiated keratinocytes. Compounds of the invention are also useful in the inhibition of kinases and are illustrated by a compound of Formula I as detailed in the Summary of the Invention. In one embodiment, with reference to compounds of Formula I, W is chosen from $-NR_4-$ and $-O-$; wherein R_4 is chosen from hydrogen and C_{1-6}alkyl.

[0018] In a further embodiment, R_1 is chosen from C_{6-10}aryl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl; wherein any arylalkyl and heteroarylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, C_{5-10}heteroaryl, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, $-XNR_5R_5$, $-XOR_5$, $-XSR_5$, $-XNR_5XNR_5R_5$, $-XNR_5XOR_5$, $-XC(O)NR_5R_5$, $-XOXR_6$ and $-XC(O)R_6$; wherein X is a bond or C_{1-6}alkylene; R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; wherein any heteroaryl substituent of R_1 is further optionally substituted by 1 to 5 C_{1-6}alkyl radicals.

[0019] In a further embodiment, R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl; wherein any arylalkyl or heteroarylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, C_{3-8}heteroarylC_{0-4}alkyl, $-XNR_5R_5$, $-XOR_5$, $-XSR_5$, $-XS(O)_2NR_5R_5$, $-XC(O)OR_5$, $-XOC(O)R_5$, $-XC(O)NR_5XNR_5R_5$, $-XC(O)NR_5XC(O)OR_5$, $-XC(O)NR_5XNR_5C(O)R_5$, $-XC(O)NR_5XNR_5C(O)OR_5$, $-XC(O)NR_5XOR_5$, $-XC(O)N(XOR_5)_2$, $-XNR_5C(O)R_5$, $-XC(O)NR_5R_6$, $-XC(O)R_6$, $-XR_7$, $-XR_6$ and $-XC(O)NR_5XR_7$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl;

R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and –C(O)OH; and R_7 is cyano.

[0020] In a further embodiment, R_3 is chosen from halo, hydroxy, $-XC(O)R_5$ and $-XC(O)OR_5$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl.

[0021] In a further embodiment, W is chosen from –NH– and –O–; and R_1 is chosen from phenyl, benzyl, 5,6,7,8-tetrahydro-naphthalenyl, benzo[1,3]dioxolyl, 1H-indazol-7-yl, indan-4-yl and 1H-indolyl; wherein any arylalkyl and heteroarylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from methoxy, methyl, amino, halo, hydroxymethyl, hydroxy, quinoxalinyl, ethyl, pyridinyl, methoxy-phenyl, piperazinyl-carbonyl, ethyl-(2-hydroxy-ethyl)-amino 2-(4-methyl-piperazin-1-yl)-ethoxy, formamyl, isopropyl, methyl-sulfanyl, tri-fluoro-methyl, ethoxy, 3-isopropylamino-propylamino, dimethyl-amino, morpholino, cyclopropyl-methoxy, butoxy, cycloheptyl-oxy and 1,4,5,7-tetramethyl-pyrrolo[3,4-d]pyridazinyl.

[0022] In a further embodiment, R_2 is chosen from pyridinyl, phenyl, thiazolyl, pyridinyl-methyl, pyridinyl-ethyl, thiophenyl, benzyl, quinolinyl, 7-oxo-5,6,7,8-tetrahydro-naphthalenyl, naphthyl and pyrimidinyl; wherein any arylalkyl or heteroarylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, methyl, propyl-sulfamoyl, methyl-sulfamoyl, methoxy, methyl-carboxy, 2-dimethylamino-ethyl-formamyl, carboxy, amino, cyano-ethyl, cyano-methyl, ethenyl, tri-fluoro-methyl, hydroxy-methyl, ethyl, methyl-sulfanyl, butyl, isobutyl, carboxy-methyl-formamidyl, 1-carboxy-ethyl-formamidyl, carboxy-ethyl, amino-ethyl-formamidyl, amino-propyl-formamidyl, dimethyl-amino-ethyl-formamidyl, dimethyl-amino-propyl-formamidyl, dimethyl-amino-butyl-formamidyl, methyl-formamidyl, ethyl-formamidyl, ethyl-formamidyl-methyl, 2-(2-dimethylamino-ethylcarbamoyl)-ethyl, 2-(2-dimethylamino-formamidyl)-ethyl, 2-(amino-ethyl-formamidyl)-ethyl, 2-(amino-propyl-formamidyl)-ethyl, 2-(propyl-formamidyl)-ethyl, amino-propyl-formamidyl-methyl, 2-(methyl-amino-carbamoyl)-ethyl, 2-(ethyl-amino-carbamoyl)-ethyl, morpholino-ethyl-formamidyl, morpholino-carbonyl-methyl, amino-ethyl-formamidyl-methyl, cyclobutyl-formamidyl, methyl-formamidyl-methyl, dimethyl-formamidyl-methyl, hydroxy-ethyl-formamidyl-methyl, hydroxy-propyl-formamidyl-methyl, N,N-bis-(3-hydroxy-propyl)-formamidyl, cyclopentyl-formamidyl, isobutyl-formamidyl, isobutyl-formamidyl-

methyl, cyclopentyl-formamidyl-methyl, cyano-ethyl-formamidyl, cyano-methyl-formamidyl, pyrrolidinyl-ethyl-formamidyl, 2-(isobutyl-formamidyl)-ethyl, 1H-tetrazolyl, 2-(1H-tetrazol-5-yl)-ethyl, 2-(1H-tetrazol-5-yl)-methyl, 2-(1-methyl-1H-tetrazol-5-yl)-methyl, acetyl-amino, cyclopropyl-formamidyl-methyl, hydroxy-ethyl-formamidyl, hydroxy-propyl-formamidyl, propyl-formamidyl-methyl, ethoxy-propyl-formamidyl, acetyl-amino-ethyl-formamidyl, 1-methyl-piperidin-4-yl-formamidyl, morpholino-carbonyl-ethyl, methoxy-carbonyl-methyl, methoxy-carbonyl-ethyl-formamidyl, methoxy-carbonyl-ethyl-formamidyl-methyl, methoxy-carbonyl-methyl-formamidyl-methyl, methoxy-carbonyl-methyl-formamidyl, 4-amino-cyclohexyl-formamidyl, 4-amino-cyclohexyl-formamidyl-methyl, acetyl-amino-ethyl-formamidyl-methyl, ethoxy-propyl-formamidyl-methyl, methoxy-carbonyl-ethyl, 1-formyl-pyrrolidin-2-yl-carboxylic acid, (1-carboxy-3-methyl-butyl)-formamidyl, 2-(methoxy-carbonyl-methyl-formamidyl)-ethyl, 1-carboxy-(2,2-dimethyl-propyl)-formamidyl, 3-tert-butoxycarbonyl-amino-propyl-formamidyl, acetoxy-methyl and 1-carboxy-ethyl-formamidyl.

[0023] In a further embodiment, n is 0 or 1; m is 0 or 1; and R_3 is chosen from halo, hydroxy,.–C(O)OH and –$C(O)OCH_3$.

[0024] In another embodiment, the present invention provides a method for inducing undifferentiated keratinocytes to differentiate into terminally differentiated keratinocytes, said method comprising contacting said undifferentiated keratinocytes with a compound chosen from 4-[2-(3-chloro-phenylamino)-pyrimidin-4-yl]-pyridine-2-carboxylic acid (2-hydroxy-ethyl)-amide, 3-[2-(3-chloro-phenylamino)-pyrimidin-4-yl]-benzonitrile, 3-[2-(3-chloro-phenylamino)-pyrimidin-4-yl]-N-(2-hydroxy-ethyl)-benzamide and 3-amino-6-hydroxy-2-phenyl-chromen-4-one.

[0025] Preferred compounds of Formula I are detailed in the Examples and Table I, *infra*. In another embodiment, the present invention provides methods for screening for compounds that induce the differentiation of undifferentiated keratinocytes into terminally differentiated keratinocytes. The method involves: (a) contacting a kinase chosen from CK2, TBK1 and NEK9 with test compounds to identify one or more compounds that modulate a biological activity of the kinase; and (b) testing the modulating compound for its ability to induce the differentiation of undifferentiated keratinocytes into terminally differentiated keratinocytes.

[0026] In another embodiment, the modulating compounds reduce the cellular level of the kinase. In a further embodiment, the modulating compounds inhibit the kinase activity. Methods for assaying cellular level of a kinase or kinase activity are well known in the art, e.g., as described in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, N.Y., Second (1989) and Third (2000) Editions; and Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., New York (1987-1999).

[0027] The effect of the modulating compound on the differentiation of undifferentiated keratinocytes into terminally differentiated keratinocytes can be tested with a variety of assays routinely practiced in the art. For example, modulatory compounds can be tested for inducing expression of a specific keratinocytes terminal differentiation marker, for example, Involucrin, filaggrin or transglutaminase. A more detailed description of quantifying the relative numbers of terminally differentiated keratinocytes after treatment with the modulating compound is given in Example 5, infra.

Pharmacology and Utility

[0028] Compounds of the invention modulate the activity of protein kinases and, as such, are useful for treating diseases or disorders in which protein kinases, particularly CK2, TBK1 and/or NEK9, contribute to the pathology and/or symptomology of the disease.

[0029] TBK1, CK2 and NEK9 are serine/threonine protein kinases that have been shown to play a role in cell cycle progression, liver regeneration, viral replication, apoptosis, transduction of growth signals, prostrate cancer, breast cancer, insulin signaling and Alzheimer's disease.

[0030] Overexpression of CK2 is associated with leukemia. In addition, inhibition of CK2 may result in the regulation of HIV-1 transcription by phosphorylating cellular proteins involved in HIV-1 trans-activation that contain multiple CK2 phosphorylation consensus sequences.

[0031] TBK1 mediates TANK's ability to activate NF-κB. NF-κB is a ubiquitously expressed transcription factor that regulates the induction of genes involved in immune and inflammatory cell function, anti-apoptotic response, and antiviral response through regulation of interferon gene expression. Inappropriate regulation of NF-κB contributes to a wide range of

human disorders, including cancers, neurodegenerative diseases, ataxia-telangiectasia, arthritis, asthma, inflammatory bowel disease, and numerous other inflammatory conditions.

[0032] Compounds of the invention, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the assays described in Example 5 and are therefore indicated for therapy. Mammalian epidermis is renewed throughout adult life by proliferation of stem cells and differentiation of their progeny. Epidermal stem cells are pluripotent, giving rise to interfollicular epidermis, sebaceous glands and all the lineages of the hair follicle. The human epidermis is a stratifying squamous epithelium comprised of a single, basally located, layer of proliferating keratinocytes and multiple suprabasal layers of differentiating keratinocytes. During differentiation, keratinocytes undergo a choreographed series of morphological and biochemical changes that result in the assembly of a protective cornified envelope.

[0033] Compounds of the invention can efficiently induce proliferating normal human epidermal keratinocytes (NHEKs) to terminally differentiate. Compounds of the invention induce the differentiation of up to 100% of undifferentiated keratinocytes into terminally differentiated keratinocytes. For example, treatment of undifferentiated keratinocytes with 330nM of compound 85 (table 1) causes a 4.2 fold (approximately 70%) increase of terminally differentiated keratinocytes after 48 hours.

[0034] Compounds of the invention can serve as useful chemical probes for study signaling pathways in epidermal stem cell differentiation and for the identification of genes and signaling pathways that play roles in the differentiation/dedifferentiation of epidermal stem cells. Compounds of the invention can also be used in novel therapeutic approaches, such as cell therapy, for the treatment of many diseases including psoriasis and cancers, for example, melanoma.

[0035] Psoriasis is one of the most common human skin disorders characterized by complex alterations of various cell types. These include epidermal keratinocyte hyper-proliferation and altered differentiation, as well as intra-epidermal accumulation of leukocytes and lymphocytic infiltration around the capillary vessels in the dermis. Psoriasis can be classified into four types: plaque-type psoriasis, guttate psoriasis, localized pustular psoriasis and generalized pustular psoriasis. The less common forms of psoriasis include pustular (localized and generalized) and erythrodermic variants. The most common form is plaque-type

psoriasis. The scale itself is variable, ranging from a thick, massive scale, as is generally seen on the scalp, to no scale at all, as is generally seen in intertriginous or partially treated areas. Guttate psoriasis is characterized by numerous small, oval (teardrop shaped) lesions that develop after an acute upper respiratory tract infection. These lesions are often not as scaly or as red as the classic lesions of plaque-type psoriasis. Usually, guttate psoriasis must be differentiated from pityriasis roseas, another indication characterized by the sudden outbreak of red scaly lesions. Compared with pityriasis roseas, psoriatic lesions are thicker and scalier, and the lesions are not usually distributed along skin oreases.

[0036] In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of the invention or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Administration and Pharmaceutical Compositions

[0037] In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

[0038] Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository

form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations may also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0039] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations). For example, synergistic effects can occur with other immunomodulatory, anti-inflammatory or any substances used in the treatment of the diseases mentioned above, for example when used in combination with cyclosporin, rapamycin, or ascomycin, or immunosuppressant analogues thereof, for example cyclosporin A (CsA), cyclosporin G, FK-506, rapamycin, or comparable

compounds, corticosteroids, cyclophosphamide, azathioprine, methotrexate, brequinar, leflunomide, mizoribine, mycophenolic acid, mycophenolate mofetil, 15-deoxyspergualin, immunosuppressant antibodies, especially monoclonal antibodies for leukocyte receptors, for example MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, CD58 or their ligands, or other immunomodulatory compounds, such as CTLA41g. Where the compounds of the invention are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

[0040] The invention also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

[0041] The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

[0042] The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

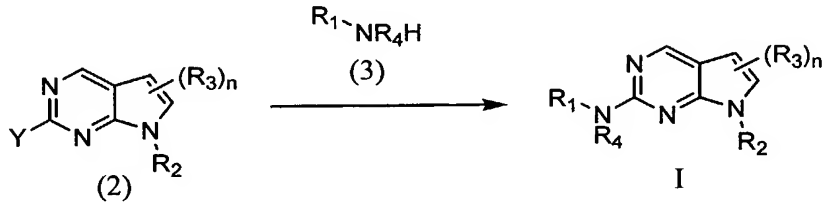
Processes for Making Compounds of the Invention

[0043] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive

functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

[0044] Compounds of Formula I, in which W is $-NR_4-$, can be prepared by proceeding as in the following Reaction Scheme I:

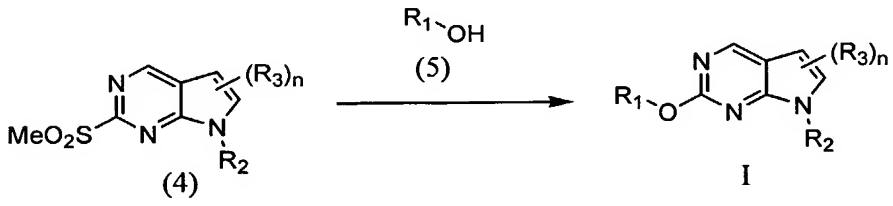
Reaction Scheme I



in which R_1, R_2, R_3, R_4 and n are as defined for Formula I in the Summary of the Invention and Y is a leaving group such as halogen (e.g. chloro, and the like). A compound of Formula Ia can be prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable base (e.g., potassium tertiary butoxide and diisopropylethyl amine, and the like), a suitable solvent (e.g., 1,4-dioxane and butanol, and the like). The reaction is carried out at 50 to 130°C and can take up to 4 hours to complete. Similarly, using appropriate starting materials, reaction with a compound of formula 3 results in compounds of Formula Ib, Ic, Id and Ie.

[0045] Compounds of Formula I, in which W is –O–, can be prepared by proceeding as in the following Reaction Scheme II:

Reaction Scheme II



in which R_1, R_2, R_3, R_4 and n are as defined for Formula I in the Summary of the Invention. A compound of Formula Ia can be prepared by reacting a compound of formula 4 with a compound of formula 5 in the presence of a suitable solvent (e.g., DMSO, and the like) and a suitable base (e.g., potassium tertiary butoxide, and the like). The reaction is carried out at 50 to 130 °C and can take up to 4 hours to complete.

[0046] Detailed descriptions of the synthesis of a compound of Formula I can be found in the Examples, *infra*.

Additional Processes for Making Compounds of the Invention

[0047] A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

[0048] The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

[0049] Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[0050] Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate

prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[0051] Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[0052] Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0053] Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[0054] In summary, the compounds of Formula I can be made by a process, which involves:

(a) that of reaction schemes I or II; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

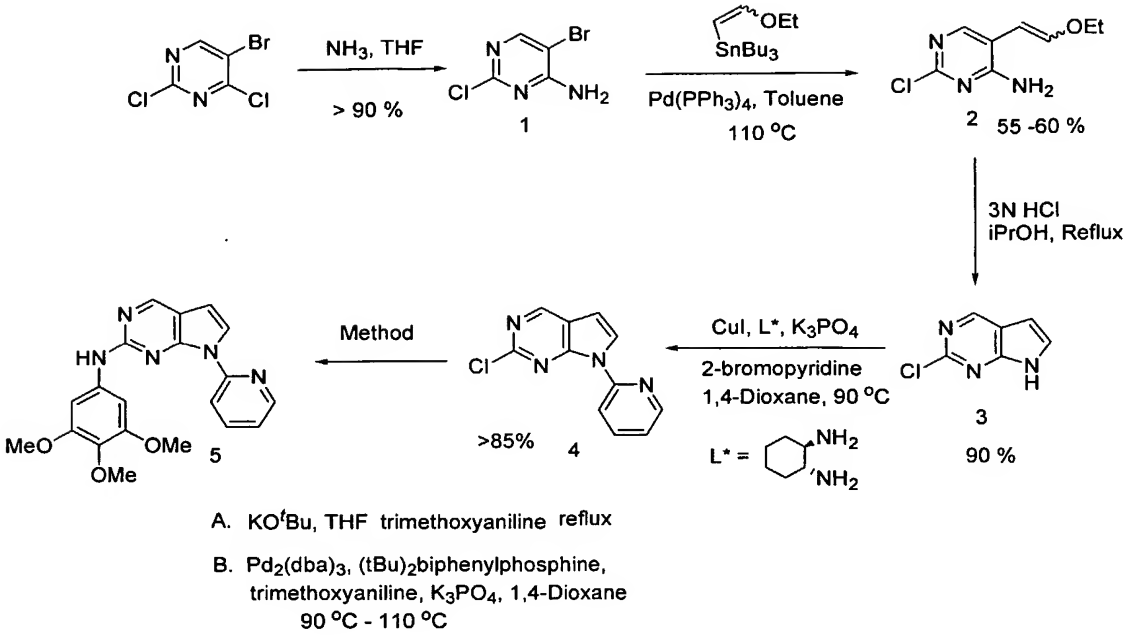
Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

[0055] The present invention is further exemplified, but not limited, by the following examples that illustrate the preparation of compounds of Formula I (Examples) and intermediates (References) according to the invention.

Example 1



[0056] **Synthesis of 5-Bromo-2-chloropyrimidin-4-ylamine (1):** A solution of 5-bromo-2,4-dichloropyrimidine (25g, 110 mmol) in 200 mL THF is treated with 47 mL of ammonia (330 mmol, 7.0M solution in methanol). After stirring for 15 hours the solution is concentrated under reduced pressure and purified by short-filtration (SiO_2, Hexanes : Ethyl acetate / 1:1) to yield 21g (92 %) of **1** as a white solid.

[0057] **Synthesis of 2-Chloro-5-(2-ethoxyvinyl)-pyrimidin-4-ylamine (2):** A 500 mL round bottomed flask is charged with 5-bromo-2-chloropyrimidin-4-ylamine (1) (10g, 48 mmol), tetrakis(triphenylphosphine)palladium(0) (2.8g, 2.5 mmol), and toluene (200 mL). Tributyl-(2-ethoxyvinyl)-stannane (22g, 60 mmol) is added and the reaction heated to 110^0C with stirring for approximately 15 hours. After cooling to room temperature, the solution is diluted with 100 mL ethyl acetate and washed with water and brine. The organic extract is dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, Hexane : Ethyl acetate / 5 :1) provides **2** (4.4 g, 46%) as a yellow solid.

[0058] **Synthesis of 2-Chloro-*7H*-pyrrolo-[2,3-*d*]pyrimidine 3:** A 500 mL round bottomed flask was charged with 2-Chloro-5-(2-ethoxyvinyl)-pyrimidin-4-ylamine **2** (4.4g, 20 mmol). Isopropanol (200 mL) is added followed by 25 mL of concentrated hydrochloric acid. The solution is heated to 90^0C and stirred for two hours. After cooling to room temperature, the

solution is concentrated under reduced pressure then basified to pH 9 with saturated aqueous $NaHCO_3$. The aqueous layer is extracted with ethyl acetate, and the organic extracts are combined and washed with saturated aqueous $NaHCO_3$ and brine. The organic extracts are dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by short-filtration (SiO_2, Hexanes : Ethyl acetate / 1 : 1) gives **3** (3.1g, 92%) as a white solid.

[0059] **Synthesis of 2-Chloro-7-pyridin-2-yl-*7H*-pyrrolo-[2,3-*d*]pyrimidine 4:** A suspension of 2-chloro-*7H*-pyrrolo-[2,3-*d*]pyrimidine **3** (0.53g, 3.5 mmol), 2-bromopyridine (0.66 mL, 1.1g, 6.9 mmol), copper(I) iodide (0.20g, 1.0 mmol), *trans*-1,2-diaminocyclohexane (0.12 mL, 0.11g, 1.0 mmol), and potassium phosphate (2.2 g, 10 mmol) in 10 mL 1,4-dioxane is heated to 100°C and stirred for four hours. The reaction mixture is cooled to room temperature, diluted with ethyl acetate, and washed with water and brine. The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, Hexane : Ethyl acetate / 5:1) provided **4** (0.69g, 87%) as a white solid.

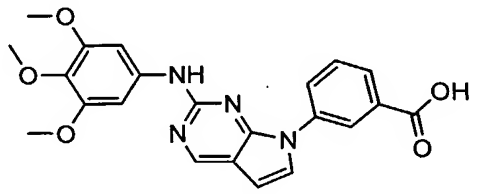
Synthesis of (7-Pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-(3,4,5-trimethoxy-phenyl)-amine (5):

[0060] Method 1. To a solution of 2-chloro-7-pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidine in 1,4-dioxane is added 3,4,5-trimethoxy aniline (3 equivalents) followed by adding potassium *tert*-butoxide solution (1.0 M in tetrahydrofuran, 3 equivalents) dropwise. After addition, the reaction mixture is heated at 80°C for 2 hours. The solvent is removed after cooling to room temperature. Purification by reverse phase HPLC gives (7-pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-(3,4,5-trimethoxy-phenyl)-amine as a white solid.

[0061] Method 2. A round bottle flask charged with 2-chloro-7-pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidine, 0.1 equivalents of tri(dibenzylideneacetone)dipalladium(0), 0.2 equivalents of biphenyl-2-yl-di-tert-butyl-phosphane, 3 equivalents of potassium phosphate and 1.5 equivalents of 3,4,5-trimethoxy aniline is flashed with nitrogen followed by the addition of 1,4-dioxane. The suspension is heated at 110°C for 18 hours. Filtration through a pad of Celite removed the solid. The filtrate is diluted with ethyl acetate, and washed with water and brine. After drying over magnesium sulfate, the product is concentrated and purified by chromatography (ethyl acetate: hexanes 1:1) to give 7-pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-(3,4,5-trimethoxy-phenyl)-amine as a white solid.

Example 2

3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoic acid

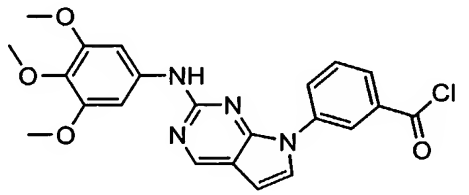


[0062] A solution of 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoic acid methyl ester in 1N sodium hydroxide (methanol: water 1:1) is stirred at room temperature for 15 hours. Acidification with 1N hydrochloric acid to pH 6 gives a precipitate.

[0063] Filtration and washing with water gives 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoic acid as a white solid.

Example 3

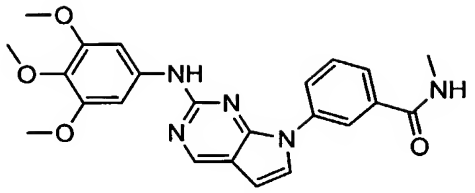
3-[2-(3,4,5-Trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoyl chloride



[0064] A dry round bottle flask charged with 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoic acid is flushed with nitrogen, dichloromethane and a few drops of *N,N'*-dimethylformamide are added. Oxalyl chloride solution (2.0 M in dichloromethane) is added dropwise. The reaction mixture is stirred at room temperature for 30 minutes, resulting in a solution of 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoyl chloride.

Example 4

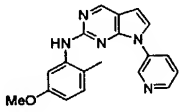
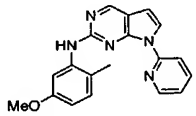
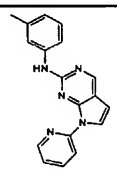
N-Methyl-3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide

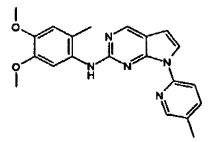
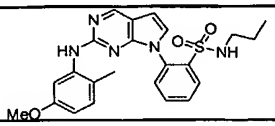
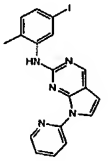
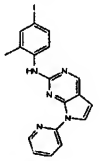
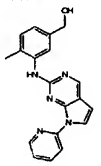
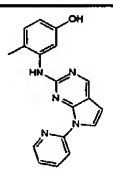
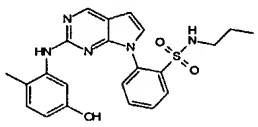
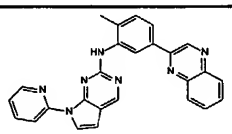
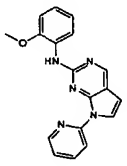


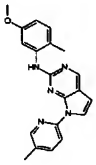
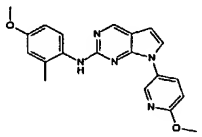
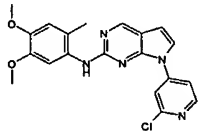
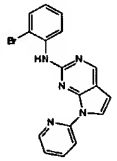
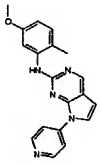
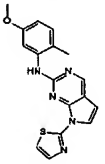
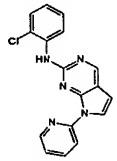
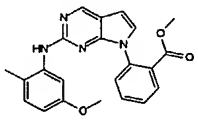
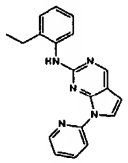
[0065] To a solution of 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoyl chloride in dichloromethane is added 5 equivalents of methylamine solution (2.0 M in tetrahydrofuran). After stirring at room temperature for 1 hour, the reaction is quenched with water. Removal of the solvent followed by purification with reverse phase HPLC gives *N*-methyl-3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide as a white solid.

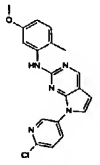
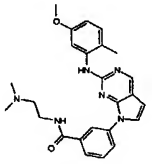
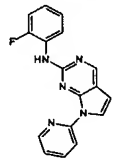
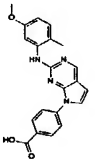
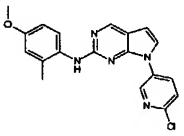
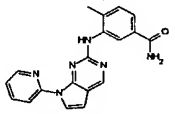
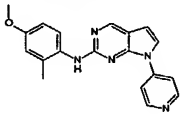
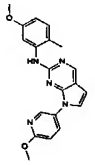
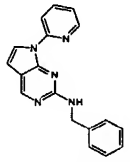
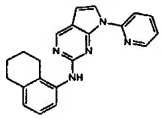
[0066] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

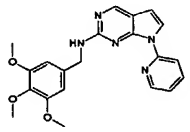
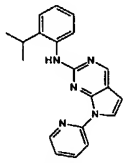
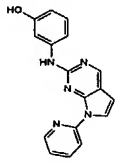
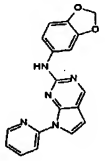
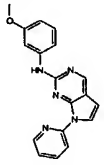
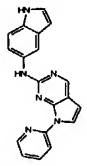
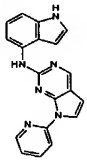
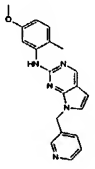
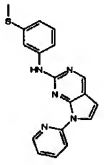
Table 1

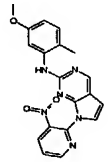
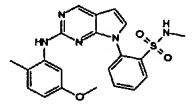
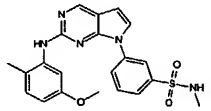
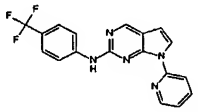
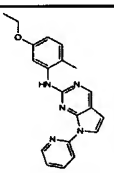
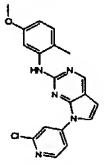
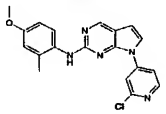
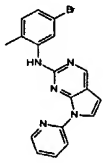
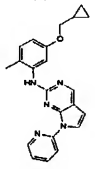
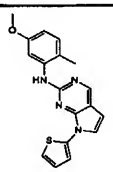
Compound Number	Structure	Physical Data ^{1}H NMR and MS (m/z)
1		MS *(m/z)* 332.3 (M+1)
2		MS *(m/z)* 332.2 (M+1)
3		MS (*m/z*) 302.2 (M+1)

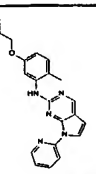
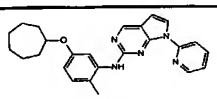
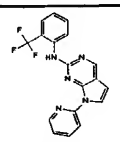
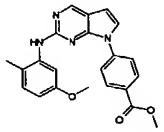
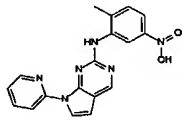
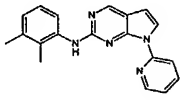
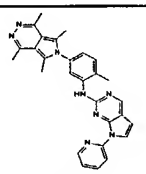
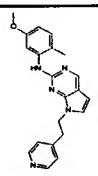
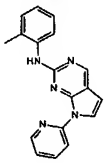
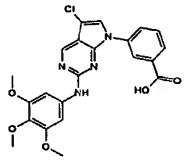
4		MS (*m/z*) 376.3 (M+1)
5		MS (*m/z*) 452.2 (M+1)
6		MS (*m/z*) 428.1 (M+1)
7		MS (*m/z*) 428.1 (M+1)
8		MS (*m/z*) 332.2 (M+1)
9		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.68 (s, 1H), 8.32 (m, 2H), 8.05 (d, 1H), 7.73 (m, 1H), 7.14 (m, 1H), 6.80 (d, 1H), 6.62 (d, 1H), 6.36 (d, 1H), 6.23 (m, 1H); MS (*m/z*) 318.2 (M+1).
10		^{1}H NMR 400 MHz ($CDCl_3$) δ 10.35 (s, 1H), 8.52 (s, 1H), 8.07 (dd, 1H), 7.70 (m, 2H), 7.37 (dd, 1H), 7.24 (d, 1H), 7.10 (d, 1H), 6.94 (d, 1H), 6.68 (d, 1H), 6.52 (dd, 1H), 5.28 (b, 1H), 3.02 (m, 2H), 2.16 (s, 3H), 1.27 (m, 2H), 0.76 (t, 3H); MS (*m/z*) 438.2 (M+1).
11		MS (*m/z*) 430.2 (M+1).
12		MS (*m/z*) 418.2 (M+1).

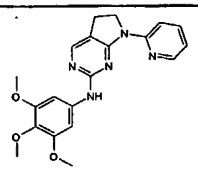
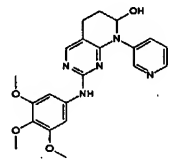
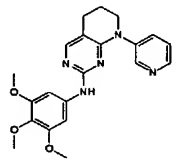
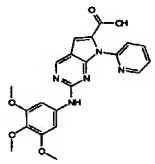
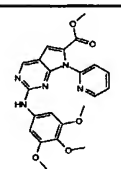
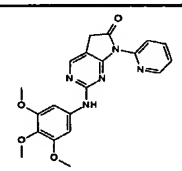
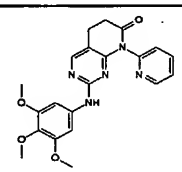
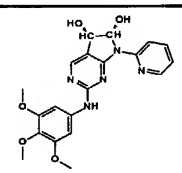
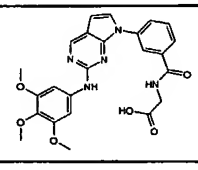
13		MS (*m/z*) 436.2 (M+1).
14		MS (*m/z*) 362.3 (M+1).
15		MS (*m/z*) 396.2 (M+1).
16		MS (*m/z*) 366.1 (M+1).
17		MS (*m/z*) 332.3 (M+1).
18		MS (*m/z*) 338.3 (M+1).
19		MS (*m/z*) 306.2 (M+1).
20		MS (*m/z*) 389.2 (M+1).
21		MS (*m/z*) 316.2 (M+1).

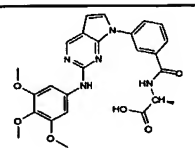
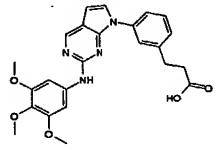
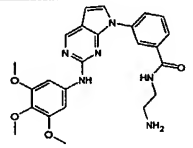
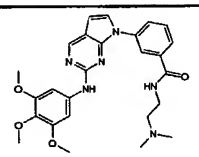
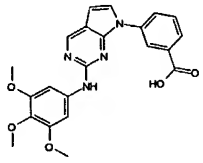
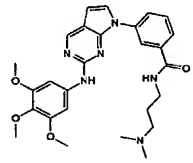
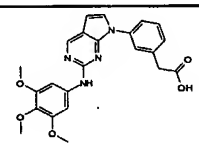
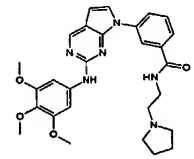
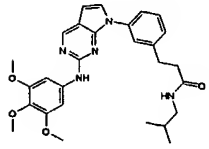
22		MS (*m/z*) 366.1 (M+1).
23		MS (*m/z*) 445.2 (M+1).
24		MS (*m/z*) 306.1 (M+1).
25		MS (*m/z*) 375.2 (M+1).
26		MS (*m/z*) 366.1 (M+1).
27		MS (*m/z*) 345.2 (M+1).
28		MS (*m/z*) 332.1 (M+1).
29		MS (*m/z*) 362.2 (M+1).
30		MS (*m/z*) 302.1 (M+1).
31		MS (*m/z*) 342.2 (M+1).

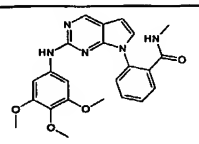
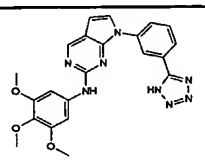
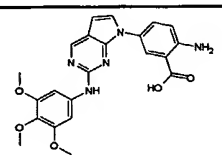
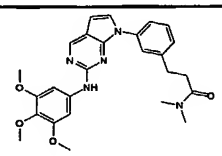
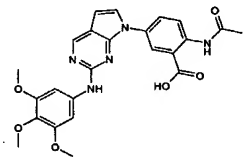
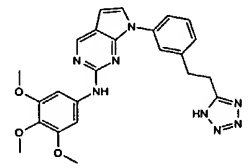
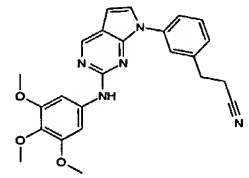
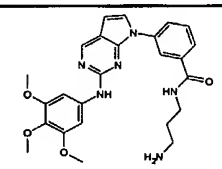
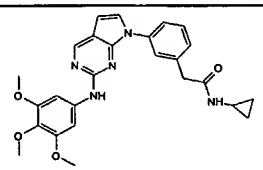
32		MS (*m/z*) 392.2 (M+1).
33		MS (*m/z*) 330.2 (M+1).
34		MS (*m/z*) 304.1 (M+1).
35		MS (*m/z*) 332.1 (M+1).
36		MS (*m/z*) 318.1 (M+1).
37		MS (*m/z*) 327.1 (M+1).
38		MS (*m/z*) 327.1 (M+1).
39		MS (*m/z*) 346.2 (M+1).
40		MS (*m/z*) 334.1 (M+1).

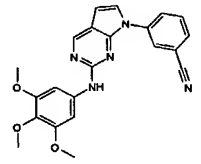
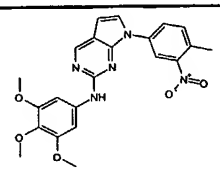
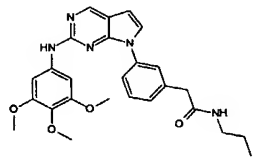
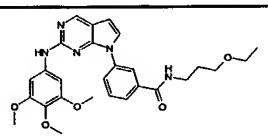
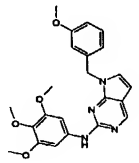
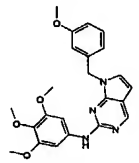
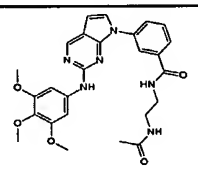
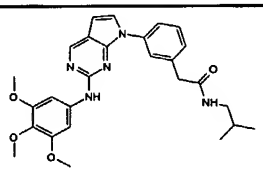
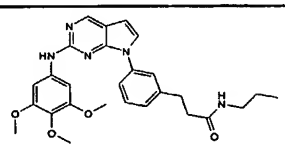
41		MS (*m/z*) 377.1 (M+1).
42		MS (*m/z*) 424.2 (M+1).
43		MS (*m/z*) 424.2 (M+1).
44		MS (*m/z*) 356.1 (M+1).
45		MS (*m/z*) 346.2 (M+1).
46		MS (*m/z*) 366.1 (M+1).
47		MS (*m/z*) 366.1 (M+1).
48		MS (*m/z*) 380.1 (M+1).
49		MS (*m/z*) 372.2 (M+1).
50		MS (*m/z*) 337.1 (M+1).

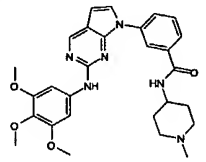
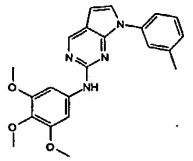
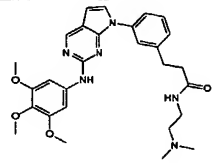
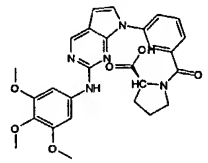
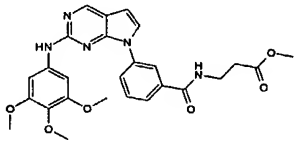
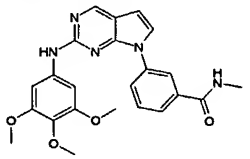
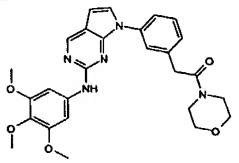
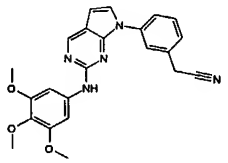
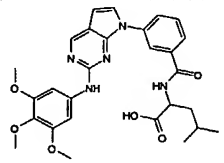
51		MS (*m/z*) 374.2 (M+1).
52		MS (*m/z*) 414.2 (M+1).
53		MS (*m/z*) 356.1 (M+1).
54		MS (*m/z*) 389.2 (M+1).
55		MS (*m/z*) 347.2 (M+1).
56		MS (*m/z*) 316.2 (M+1).
57		MS (*m/z*) 475.2 (M+1).
58		MS (*m/z*) 360.2 (M+1).
59		MS (*m/z*) 302.2 (M+1).
60		MS (*m/z*) 375.2 (M+1).

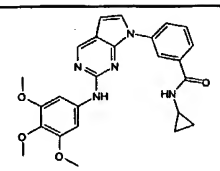
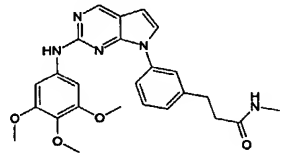
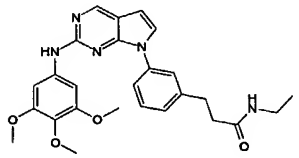
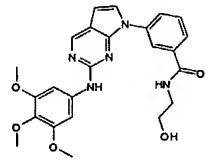
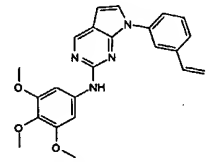
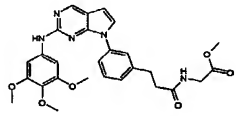
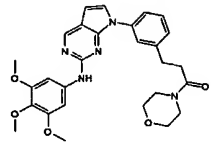
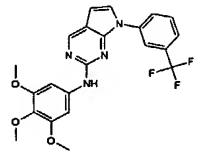
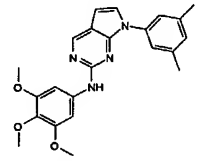
61		MS (*m/z*) 379.9 (M+1).
62		MS (*m/z*) 410.5 (M+1).
63		MS (*m/z*) 394.4 (M+1).
64		MS (*m/z*) 422.1 (M+1).
65		MS (*m/z*) 436.2 (M+1).
66		MS (*m/z*) 394.4 (M+1).
67		MS (*m/z*) 408.4 (M+1).
68		MS (*m/z*) 412.2 (M+1).
69		MS (*m/z*) 477.8 (M+1).

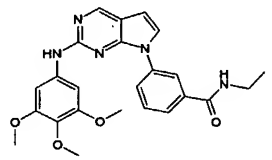
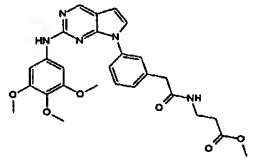
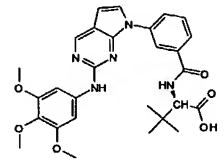
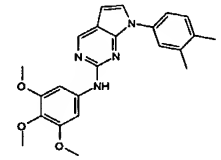
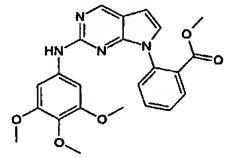
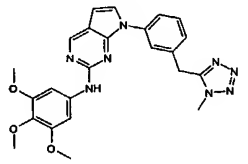
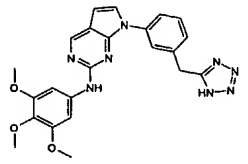
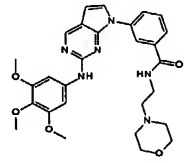
70		MS (*m/z*) 492.2 (M+1).
71		^{1}H NMR 400 MHz (DMSO-d_6) δ 9.31 (s, 1H), 8.75 (s, 1H), 7.65 (m, 1H), 7.53 (s, 1H), 7.51 (d, 1H), 7.39 (t, 1H), 7.21 (m, 1H), 7.13 (s, 2H), 6.61 (d, 1H), 5.83 (s, 1H), 3.53 (d, 9H), 2.85 (m, 2H), 2.54 (m,2H); MS (*m/z*) 449.0 (M+1).
72		MS (*m/z*) 463.2 (M+1).
73		MS (*m/z*) 491.2 (M+1).
74		^{1}H NMR 400 MHz (DMSO-d_6) δ 9.30 (s, 1H), 8.73 (s, 1H), 8.13 (m, 1H), 8.02 (m, 1H), 7.87 (m, 1H), 7.59 (t, 1H), 7.55 (d, 1H), 7.09 (s, 2H), 6.61 (d, 1H), 5.77 (s, 1H), 3.48 (d, 9H); MS (*m/z*) 421.1 (M+1).
75		MS (*m/z*) 505.3 (M+1).
76		^{1}H NMR 400 MHz (DMSO-d_6) δ 9.35 (s, 1H), 8.80 (s, 1H), 7.73 (d, 1H), 7.60 (s, 1H), 7.53 (d, 1H), 7.45 (t, 1H), 7.28 (d, 1H), 7.19 (s, 2H), 6.67 (d, 1H), 3.59 (m, 11H); MS (*m/z*) 435.2 (M+1).
77		MS (*m/z*) 516.3 (M+1).
78		MS (*m/z*) 504.3 (M+1).

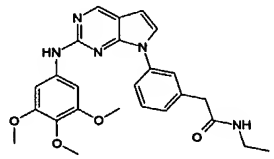
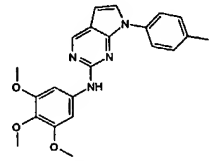
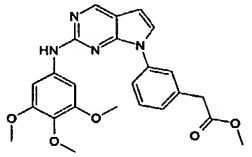
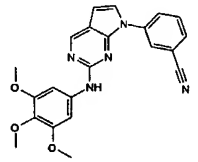
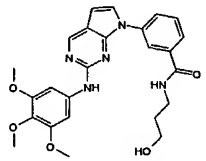
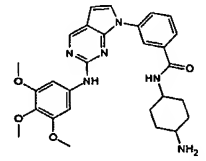
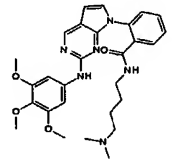
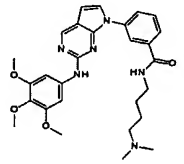
79		MS (*m/z*) 434.2 (M+1).
80		^{1}H NMR 400 MHz (MeOH-d_4) δ 8.76 (s, 1H), 8.57 (t, 1H), 8.10 (m, 1H), 8.02 (m, 1H), 7.77 (m,2H), 6.97 (s, 2H), 6.86 (d, 1H), 3.69 (d, 9H); MS (*m/z*) 445.2 (M+1).
81		MS (*m/z*) 436.2 (M+1).
82		MS (*m/z*) 476.2 (M+1).
83		^{1}H NMR 400 MHz (DMSO-d_6) δ 11.17 (s, 1H), 9.53 (s, 1H), 8.94 (s, 1H), 8.72 (m, 1H), 8.33 (d, 1H), 8.17 (m, 1H), 7.71 (d, 1H), 7.32 (s, 2H), 6.81 (d, 1H), 3.72 (d, 9H), 2.33 (s, 3H); MS (*m/z*) 478.2 (M+1).
84		^{1}H NMR 400 MHz ($CDCl_3$) δ 11.6 (s, 1H), 8.48 (s, 1H), 7.69 (m, 1H), 7.46 (m, 2H), 7.33 (m, 1H), 7.25 (m, 1H), 6.73 (m, 3H), 3.98 (s, 3H), 3.66 (d, 6H), 3.09 (m, 2H), 2.92 (m, 2H); MS (*m/z*) 473.3 (M+1).
85		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.74 (s, 1H), 7.70 (m, 1H), 7.49 (t, 1H), 7.27 (d, 1H), 7.23 (m, 1H), 6.98 (d, 2H), 6.61 (d, 1H), 3.91 (s, 3H), 3.77 (s, 6H), 3.07 (m, 2H), 2.70 (m, 2H); MS (*m/z*) 430.2 (M+1).
86		MS (*m/z*) 477.2 (M+1).
87		MS (*m/z*) 474.2 (M+1).

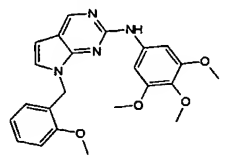
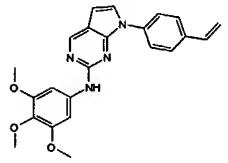
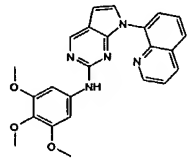
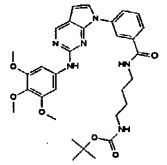
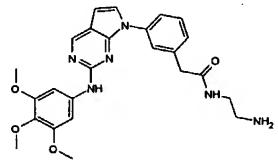
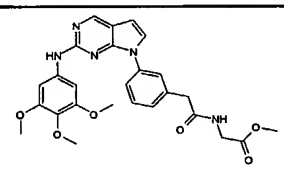
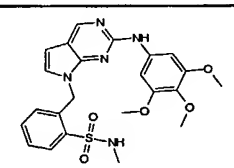
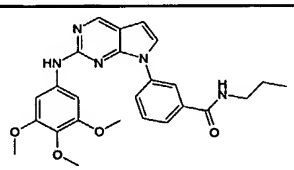
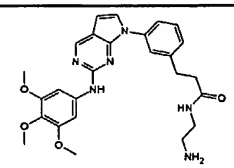
88		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.67 (s, 1H), 8.02 (m, 2H), 7.55 (m, 2H), 7.16 (d. 1H), 6.86 (s, 2H), 6.56 (d, 1H), 3.85 (s, 3H), 3.72 (s, 6H); MS (*m/z*) 402.1 (M+1).
89		MS (*m/z*) 436.1 (M+1).
90		MS (*m/z*) 476.2 (M+1).
91		MS (*m/z*) 506.3 (M+1).
92		MS (*m/z*) 421.2 (M+1).
93		MS (*m/z*) 421.2 (M+1).
94		MS (*m/z*) 505.3 (M+1).
95		MS (*m/z*) 490.2 (M+1).
96		MS (*m/z*) 490.2 (M+1).

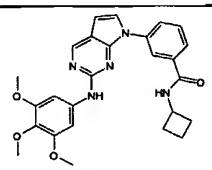
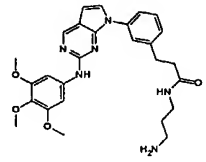
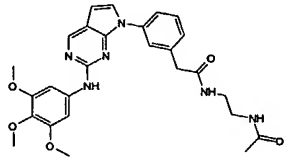
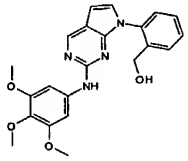
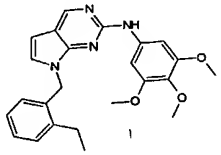
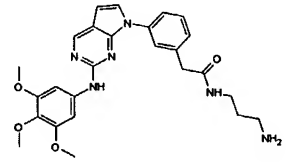
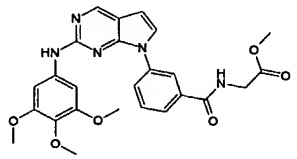
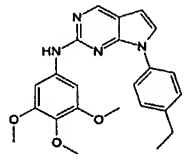
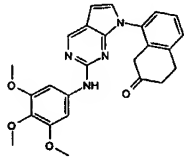
97		MS (*m/z*) 517.3 (M+1).
98		MS (*m/z*) 391.2 (M+1).
99		MS (*m/z*) 519.3 (M+1).
100		MS (*m/z*) 518.2 (M+1).
101		MS (*m/z*) 506.2 (M+1).
102		MS (*m/z*) 434.2 (M+1).
103		MS (*m/z*) 504.2 (M+1).
104		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.87 (s, 1H), 7.92 (m, 1H), 7.86 (m, 1H), 7.66 (t, 1H), 7.48 (m, 1H), 7.39 (d, 1H), 7.22 (s, 1H), 7.09 (s, 2H), 6.75 (d, 1H), 3.96 (s, 3H), 3.88 (s, 6H); MS (*m/z*) 415.9 (M+1).
105		MS (*m/z*) 534.2 (M+1).

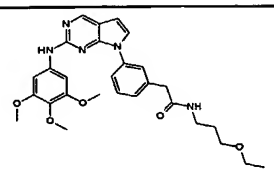
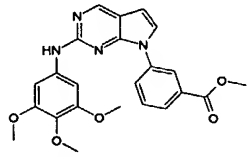
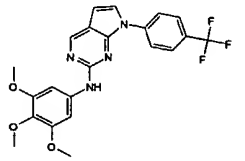
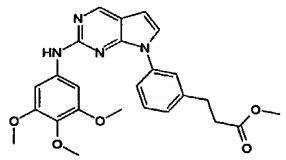
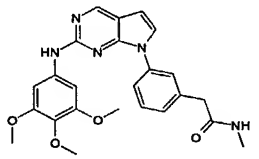
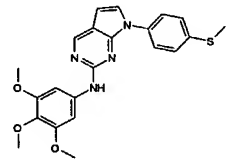
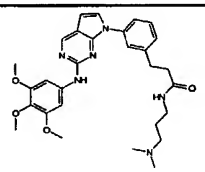
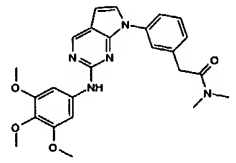
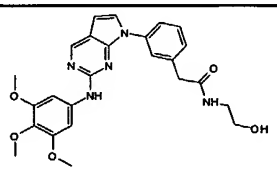
106		MS (*m/z*) 460.2 (M+1).
107		MS (*m/z*) 462.2 (M+1).
108		MS (*m/z*) 476.2 (M+1).
109		MS (*m/z*) 464.2 (M+1).
110		MS (*m/z*) 445.1 (M+1).
111		MS (*m/z*) 520.2 (M+1).
112		MS (*m/z*) 517.2 (M+1).
113		MS (*m/z*) 403.2 (M+1).
114		MS (*m/z*) 405.2 (M+1).

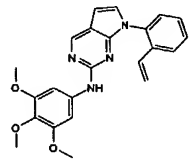
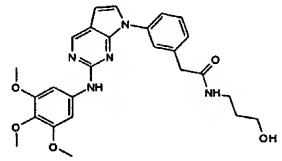
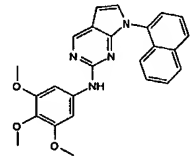
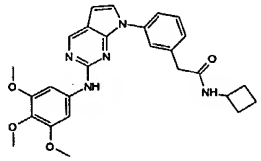
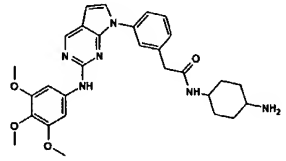
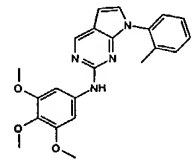
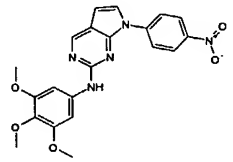
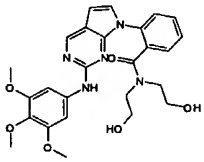
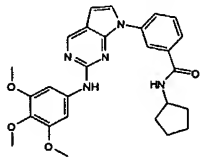
115		MS (*m/z*) 478.2 (M+1).
116		MS (*m/z*) 520.2 (M+1).
117		MS (*m/z*) 534.2 (M+1).
118		MS (*m/z*) 405.2 (M+1).
119		MS (*m/z*) 419.2 (M+1).
120		^{1}H NMR 400 MHz (MeOH-d_4) δ 8.61 (s, 1H), 7.64 (m, 2H), 7.49 (d, 1H), 7.43 (t, 1H), 7.22 (d, 1H), 6.90 (s, 2H), 6.63 (d, 1H), 4.31 (s, 2H), 3.90 (s, 3H), 3.62 (s, 3H), 3.56 (s, 6H); MS (*m/z*) 473.5 (M+1).
121		^{1}H NMR 400 MHz (MeOH-d_4) δ 8.62 (s, 1H), 7.65 (m, 1H), 7.63 (m, 1H), 7.54 (d, 1H), 7.43 (m, 1H), 7.26 (m, 1H), 6.86 (s, 2H), 6069 (d, 1H), 4.31 (s, 2H), 3.63 (s, 3H), 3.58 (s, 6H); MS (m/z) 415.9 (M+1). MS (*m/z*) 459.2 (M+1).
122		MS (*m/z*) 533.2 (M+1).

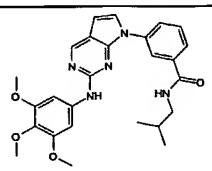
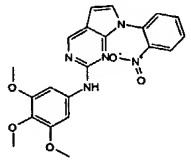
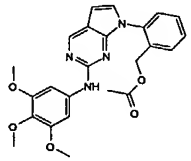
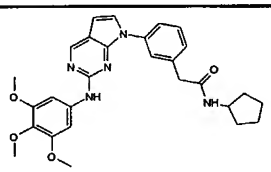
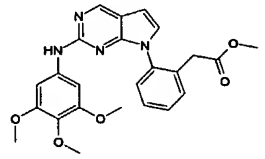
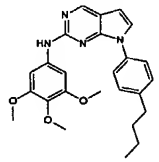
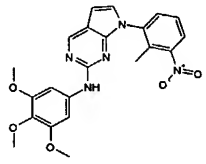
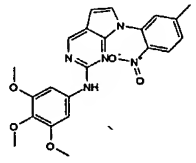
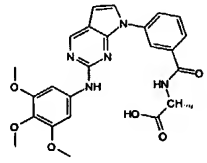
123		MS (*m/z*) 462.2 (M+1).
124		MS (*m/z*) 391.2 (M+1).
125		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.78 (s, 1H), 7.71 (m, 1H), 7.56 (m, 1H), 7.44 (t, 1H), 7.27 (m, 1H), 7.21 (d, 1H), 7.13 (b, 1H), 6.95 (s, 2H), 6.57 (d, 1H), 3.80 (s, 2H), 3.79 (s, 3H), 3.70 (m, 9H); MS (*m/z*) 449.3 (M+1).
126		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.67 (s, 1H), 8.04 (m, 1H), 8.01 (m, 1H), 7.55 (m, 2H), 7.16 (d, 1H), 7.07 (s, 1H), 6.87 (s, 2H), 6.57 (d, 1H), 3.76 (s, 3H), 3.71 (d, 6H); MS (*m/z*) 503.2 (M+1).
127		MS (*m/z*) 478.2 (M+1).
128		MS (*m/z*) 517.3 (M+1).
129		MS (*m/z*) 519.2 (M+1).
130		MS (*m/z*) 519.3 (M+1).

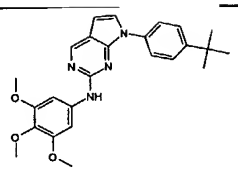
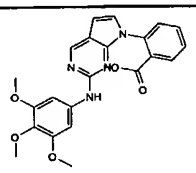
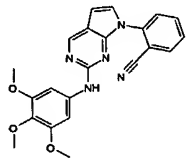
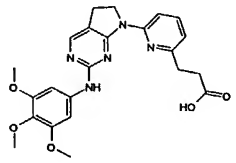
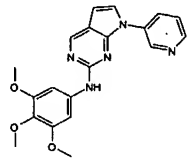
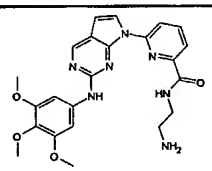
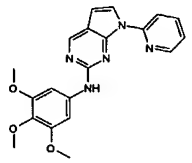
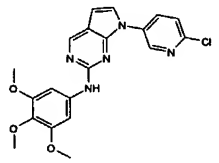
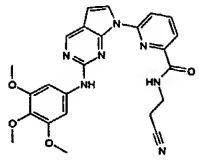
131		MS (*m/z*) 421.2 (M+1).
132		MS (*m/z*) 403.2 (M+1).
133		MS (*m/z*) 427.9 (M+1).
134		MS (*m/z*) 591.3 (M+1).
135		MS (*m/z*) 477.2 (M+1).
136		MS (*m/z*) 506.2 (M+1).
137		MS (*m/z*) 484.2 (M+1).
138		MS (*m/z*) 462.2 (M+1).
139		MS (*m/z*) 491.2 (M+1).

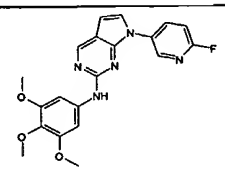
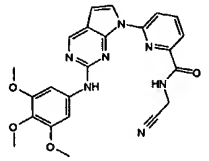
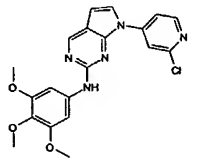
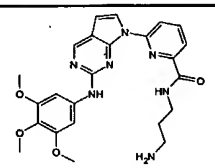
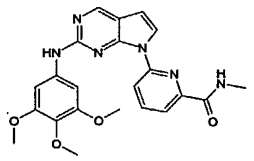
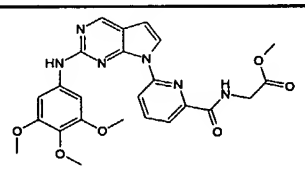
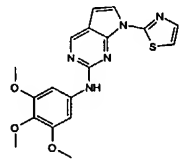
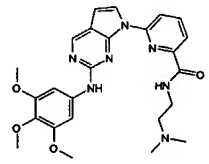
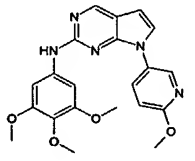
140		MS (*m/z*) 474.2 (M+1).
141		MS (*m/z*) 505.3(M+1).
142		MS (*m/z*) 519.2 (M+1).
143		MS (*m/z*) 407.3 (M+1).
144		MS (*m/z*) 419.2 (M+1).
145		MS (*m/z*) 491.2 (M+1).
146		MS (*m/z*) 492.2 (M+1).
147		MS (*m/z*) 405.2 (M+1).
148		MS (*m/z*) 444.9 (M+1).

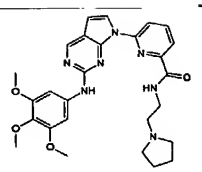
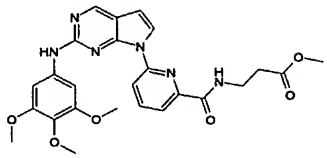
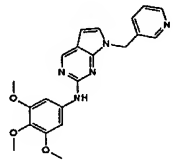
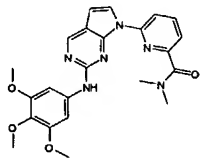
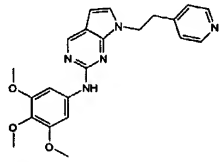
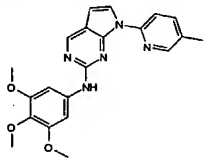
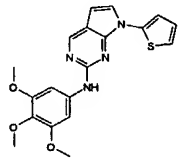
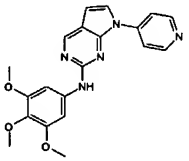
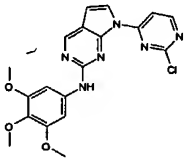
149		MS (*m/z*) 520.3 (M+1).
150		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.71 (s, 1H), 8.29 (t, 1H), 8.08 (m, 1H), 8.01 (m, 1H), 7.57 (t, 1H), 7.26 (d, 1H), 7.18 (s, 1H), 6.93 (s, 2H), 6.60 (d, 1H), 3.93 (s, 3H), 3.80 (d, 9H); MS (*m/z*) 435.3 (M+1).
151		MS (*m/z*) 445.1 (M+1).
152		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.64 (s, 1H), 7.56 (m, 1H), 7.41 (m, 1H), 7.33 (t, 1H), 7.12 (m, 2H), 6.90 (s, 2H), 6.50 (d, 1H), 3.73 (s, 3H), 3.65 (s, 6H), 3.60 (s, 3H), 2.97 (m, 2H), 2.60 (m, 2H); MS (*m/z*) 463.1 (M+1).
153		MS (*m/z*) 478.2 (M+1).
154		MS (*m/z*) 423.1 (M+1).
155		MS (*m/z*) 533.3 (M+1).
156		MS (*m/z*) 462.2 (M+1).
157		MS (*m/z*) 478.2 (M+1).

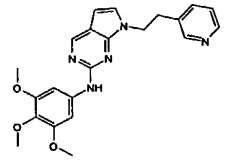
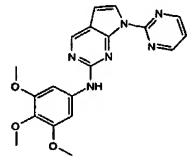
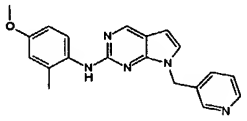
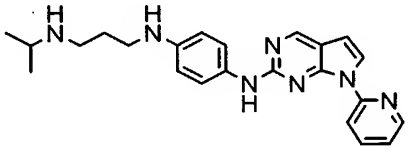
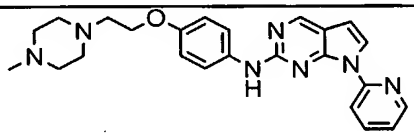
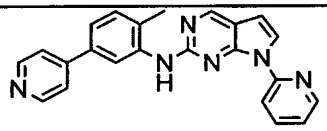
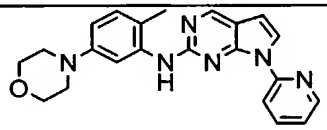
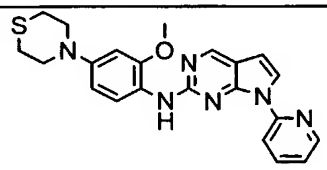
158		MS (*m/z*) 403.2 (M+1).
159		MS (*m/z*) 492.2 (M+1).
160		MS (*m/z*) 427.2 (M+1).
161		MS (*m/z*) 488.2 (M+1).
162		MS (*m/z*) 531.3 (M+1).
163		MS (*m/z*) 391.2 (M+1).
164		MS (*m/z*) 422.1 (M+1).
165		MS (*m/z*) 508.2 (M+1).
166		MS (*m/z*) 488.2 (M+1).

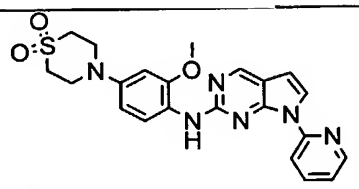
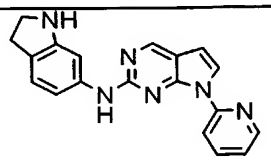
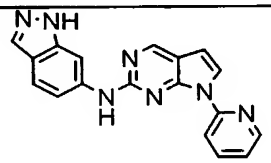
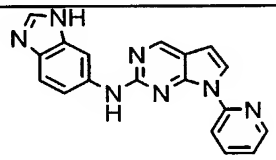
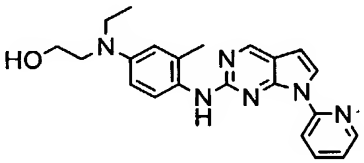
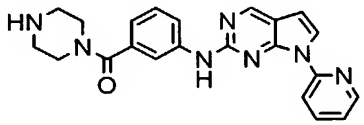
167		MS (*m/z*) 476.2 (M+1).
168		MS (*m/z*) 422.1 (M+1).
169		MS (*m/z*) 450.3 (M+1).
170		MS (*m/z*) 502.2 (M+1).
171		MS (*m/z*) 448.9 (M+1).
172		MS (*m/z*) 433.2M+1).
173		MS (*m/z*) 436.1 (M+1).
174		MS (*m/z*) 436.1 (M+1).
175		MS (*m/z*) 492.2 (M+1).

176		MS (*m/z*) 33.2 (M+1).
177		MS (*m/z*) 421.2 (M+1).
178		MS (*m/z*) 402.2 (M+1).
179		MS (*m/z*) 452.2 (M+1).
180		MS (*m/z*) 378.2 (M+1).
181		MS (*m/z*) 464.1 (M+1).
182		MS (*m/z*) 378.2 (M+1).
183		MS (*m/z*) 411.11 (M+1).
184		MS (*m/z*) 474.1 (M+1).

185		MS (*m/z*) 396.1 (M+1).
186		MS (*m/z*) 460.1 (M+1).
187		MS (*m/z*) 412.1 (M+1).
188		MS (*m/z*) 478.2 (M+1).
189		MS (*m/z*) 435.1 (M+1).
190		MS (*m/z*) 493.10 (M+1).
191		MS (*m/z*) 384.1 (M+1).
192		MS (*m/z*) 492.2 (M+1).
193		MS (*m/z*) 408.2 (M+1).

194		MS (*m/z*) 518.20 (M+1).
195		MS (*m/z*) 507.15 (M+1).
196		MS (*m/z*) 392.20 (M+1).
197		MS (*m/z*) 449.10 (M+1).
198		MS (*m/z*) 406.2 (M+1).
199		MS (*m/z*) 392.2 (M+1).
200		MS (*m/z*) 383.1 (M+1).
201		MS (*m/z*) 378.2 (M+1).
202		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.72 (d, 1H), 8.48 (s, 1H), 8.16 (d, 1H), 7.30 (d, 1H), 7.16 (s, 2H), 6.72 (d, 1H), 3.89 (s, 6H), 3.85 (s, 3H); MS (*m/z*) 413.1 (M+1).

203		MS (m/z) 406.3 (M+1).
204		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.85 (d, 2H), 8.74 (s, 1H), 8.03 (d, 1H), 7.32 (s, 1H), 7.25 (t, 1H), 7.13 (s, 2H), 6.63 (d, 1H), 3.93 (s, 6H), 3.86 (s, 3H); MS (*m/z*) 379.4 (M+1).
205		MS (*m/z*) 346.2 (M+1).
206		
208		
209		
210		
211		

212		
213		
214		
215		
216		
217		

Example 5 - Assays

[0067] The ability of the compounds of the invention to induce the differentiation of undifferentiated keratinocytes into terminally differentiated keratinocytes was measured by monitoring the expression of the keratinocyte differentiation marker, involucrin.

[0068] Normal human epidermal keratinocyte (NHEK) cultures are purchased from Cambrex (Walkersville, MD) and expanded in the KGM-2 medium according to the method

described in the manufacturer's protocol (Epidermal Keratinocyte Cell Systems-Instructions, AA-1000-5 Rev. 12/02). Cells of the third passage are used in all experiments.

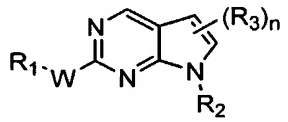
[0069] For reporter gene assays with transiently transfected cells, the cells are typically transfected in 150-mm diameter dishes when 30-40% confluent. A reporter plasmid (18.4 μg), 3.7-kb INV promoter-luciferase construct, is transfected into the normal human epidermal keratinocytes using FuGENE 6 (Roche) following the manufacturer's protocol. After 24 hours, the transfected cells are plated into 96-well assay plates and incubated for 24 hours. The cells are treated with an appropriate amount of a compound of the invention and incubated for a further 2 days. The reported gene activity in the cells is measured using the Bright-Glo™ luciferase assay system (Promega) and an Analyst® AD system (Molecular Devices).

[0070] The induction of luciferase activity of transfected NHEKs in 1.4mM $CaCl_2$ was used as a positive control and no treatment of NHEKs is used as a baseline measurement. NHEKs transfected with the reporter plasmid exhibits a 5-fold induction of the luciferase activity when incubated with medium containing 1.4 mM $CaCl_2$ for 48 hours, compared to cells that are maintained in medium with 0.03 mM $CaCl_2$.

[0071] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A method for inducing undifferentiated keratinocytes to differentiate into terminally differentiated keratinocytes, said method comprising contacting said undifferentiated keratinocytes with a compound of Formula I:



I

in which:

n is chosen from 0, 1 and 2; m is chosen from 0, 1, 2 and 3;

W is chosen from $-NR_4-$, $-S-$, $-O-$, $-S(O)-$ and $-S(O)_2-$; wherein R_4 is chosen from hydrogen and C_{1-6}alkyl;

R_1 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-XNR_5R_5$, $-XNR_5XNR_5R_5$, $-XNR_5XOR_5$, $-XOR_5$, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XC(O)NR_5R_5$, $-XOXR_6$ and $-XC(O)R_6$; wherein X is a bond or C_{1-6}alkylene; R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent of R_1 is further optionally substituted by 1 to 5 radicals independently chosen from C_{1-6}alkyl and C_{1-6}alkoxy;

R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-8}heteroarylC_{0-4}alkyl, $-XNR_5R_5$, –

XOR_5, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XSNR_5R_5$, $-XS(O)NR_5R_5$, $-XS(O)_2NR_5R_5$, $-XC(O)OR_5$, $-XOC(O)R_5$, $-XC(O)R_5$, $-XC(O)NR_5XNR_5R_5$, $-XC(O)NR_5R_5$, $-XC(O)NR_5XC(O)OR_5$, $-XC(O)NR_5XNR_5C(O)R_5$, $-XC(O)NR_5XNR_5C(O)OR_5$, $-XC(O)NR_5XOR_5$, $-XC(O)N(XOR_5)_2$, $-XNR_5C(O)R_5$, $-XC(O)NR_5R_6$, $-XC(O)R_6$, $-XR_7$, $-XC(O)R_7$, $-XR_6$ and $-XC(O)NR_5XR_7$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; and R_7 is chosen from halo and cyano;

R_3 is chosen from halo, hydroxy, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XC(O)R_5$ and $-XC(O)OR_5$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which:

W is chosen from $-NR_4-$ and $-O-$; wherein R_4 is chosen from hydrogen and C_{1-6}alkyl;

R_1 is chosen from C_{6-10}aryl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl; wherein any arylalkyl and heteroarylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, C_{5-10}heteroaryl, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, $-XNR_5R_5$, $-XOR_5$, $-XSR_5$, $-XNR_5XNR_5R_5$, $-XNR_5XOR_5$, $-XC(O)NR_5R_5$, $-XOXR_6$ and $-XC(O)R_6$; wherein X is a bond or C_{1-6}alkylene; R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; wherein any heteroaryl substituent of R_1 is further optionally substituted by 1 to 5 C_{1-6}alkyl radicals;

R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl; wherein any arylalkyl or heteroarylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, C_{3-8}heteroarylC_{0-4}alkyl, $-XNR_5R_5$, $-XOR_5$, $-XSR_5$, $-XS(O)_2NR_5R_5$, $-XC(O)OR_5$, $-XOC(O)R_5$, $-XC(O)NR_5XNR_5R_5$, $-XC(O)NR_5XC(O)OR_5$,$-$ $XC(O)NR_5XNR_5C(O)R_5$, $-XC(O)NR_5XNR_5C(O)OR_5$, $-XC(O)NR_5XOR_5$, $-XC(O)N(XOR_5)_2$, $-XNR_5C(O)R_5$, $-XC(O)NR_5R_6$, $-XC(O)R_6$, $-XR_7$, $-XR_6$ and $-XC(O)NR_5XR_7$; wherein X is a bond or C_{1-}

$_{6}$alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and –C(O)OH; and R_7 is cyano; and

R_3 is chosen from halo, hydroxy, –XC(O)R_5 and –XC(O)OR_5; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl.

3. The compound of claim 1 in which W is chosen from –NH– and –O–; and R_1 is chosen from phenyl, benzyl, 5,6,7,8-tetrahydro-naphthalenyl, benzo[1,3]dioxolyl, 1H-indazol-7-yl, indan-4-yl and 1H-indolyl; wherein any arylalkyl and heteroarylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from methoxy, methyl, amino, halo, hydroxymethyl, hydroxy, quinoxalinyl, ethyl, pyridinyl, methoxy-phenyl, piperazinyl-carbonyl, ethyl-(2-hydroxy-ethyl)-amino 2-(4-methyl-piperazin-1-yl)-ethoxy, formamyl, isopropyl, methyl-sulfanyl, tri-fluoro-methyl, ethoxy, 3-isopropylamino-propylamino, dimethyl-amino, morpholino, cyclopropyl-methoxy, butoxy, cycloheptyl-oxy and 1,4,5,7-tetramethyl-pyrrolo[3,4-d]pyridazinyl.

4. The compound of claim 1 in which R_2 is chosen from pyridinyl, phenyl, thiazolyl, pyridinyl-methyl, pyridinyl-ethyl, thiophenyl, benzyl, quinolinyl, 7-oxo-5,6,7,8-tetrahydro-naphthalenyl, naphthyl and pyrimidinyl; wherein any arylalkyl or heteroarylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, methyl, propyl-sulfamoyl, methyl-sulfamoyl, methoxy, methyl-carboxy, 2-dimethylamino-ethyl-formamyl, carboxy, amino, cyano-ethyl, cyano-methyl, ethenyl, tri-fluoro-methyl, hydroxy-methyl, ethyl, methyl-sulfanyl, butyl, isobutyl, carboxy-methyl-formamidyl, 1-carboxy-ethyl-formamidyl, carboxy-ethyl, amino-ethyl-formamidyl, amino-propyl-formamidyl, dimethyl-amino-ethyl-formamidyl, dimethyl-amino-propyl-formamidyl, dimethyl-amino-butyl-formamidyl, methyl-formamidyl, ethyl-formamidyl, ethyl-formamidyl-methyl, 2-(2-dimethylamino-ethylcarbamoyl)-ethyl, 2-(2-dimethylamino-formamidyl)-ethyl, 2-(amino-ethyl-formamidyl)-ethyl, 2-(amino-propyl-formamidyl)-ethyl, 2-(propyl-formamidyl)-ethyl, amino-propyl-formamidyl-methyl, 2-(methyl-amino-carbamoyl)-ethyl, 2-(ethyl-amino-carbamoyl)-ethyl, morpholino-ethyl-formamidyl, morpholino-carbonyl-methyl, amino-ethyl-formamidyl-methyl, cyclobutyl-formamidyl, methyl-formamidyl-methyl, dimethyl-formamidyl-methyl,

hydroxy-ethyl-formamidyl-methyl, hydroxy-propyl-formamidyl-methyl, N,N-bis-(3-hydroxy-propyl)-formamidyl, cyclopentyl-formamidyl, isobutyl-formamidyl, isobutyl-formamidyl-methyl, cyclopentyl-formamidyl-methyl, cyano-ethyl-formamidyl, cyano-methyl-formamidyl, pyrrolidinyl-ethyl-formamidyl, 2-(isobutyl-formamidyl)-ethyl, 1H-tetrazolyl, 2-(1H-tetrazol-5-yl)-ethyl, 2-(1H-tetrazol-5-yl)-methyl, 2-(1-methyl-1H-tetrazol-5-yl)-methyl, acetyl-amino, cyclopropyl-formamidyl-methyl, hydroxy-ethyl-formamidyl, hydroxy-propyl-formamidyl, propyl-formamidyl-methyl, ethoxy-propyl-formamidyl, acetyl-amino-ethyl-formamidyl, 1-methyl-piperidin-4-yl-formamidyl, morpholino-carbonyl-ethyl, methoxy-carbonyl-methyl, methoxy-carbonyl-ethyl-formamidyl, methoxy-carbonyl-ethyl-formamidyl-methyl, methoxy-carbonyl-methyl-formamidyl-methyl, methoxy-carbonyl-methyl-formamidyl, 4-amino-cyclohexyl-formamidyl, 4-amino-cyclohexyl-formamidyl-methyl, acetyl-amino-ethyl-formamidyl-methyl, ethoxy-propyl-formamidyl-methyl, methoxy-carbonyl-ethyl, 1-formyl-pyrrolidin-2-yl-carboxylic acid, (1-carboxy-3-methyl-butyl)-formamidyl, 2-(methoxy-carbonyl-methyl-formamidyl)-ethyl, 1-carboxy-(2,2-dimethyl-propyl)-formamidyl, 3-tert-butoxycarbonyl-amino-propyl-formamidyl, acetoxy-methyl and 1-carboxy-ethyl-formamidyl.

5. The compound of claim 1 in which n is 0 or 1; m is 0 or 1; and R_3 is chosen from halo, hydroxy, –C(O)OH and $–C(O)OCH_3$.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

7. A method for treating a disease in an animal in which inhibition of kinase activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

8. The method of claim 7 in which the kinase is chosen from CK2, TBK1 and NEK9.

9. The use of a compound of claim 1 in the manufacture of a medicament for treating a disease in an animal in which the kinase activity of CK2, TBK1 and/or NEK9 contributes to the pathology and/or symptomology of the disease.

10. A method for screening for compounds that induce the differentiation of undifferentiated keratinocytes into terminally differentiated keratinocytes: (a) contacting a kinase chosen from CK2, TBK1 and NEK9 with test compounds to identify one or more compounds that modulate a biological activity of the kinase; and (b) testing the modulating compounds for its ability to induce the differentiation of undifferentiated keratinocytes into terminally differentiated keratinocytes.

11. The method of claim 10 wherein the modulating compound inhibits the kinase

12. The method of claim 10 wherein the testing comprises assaying expression of a terminally differentiated keratinocyte marker in the presence of the modulating compounds.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/15118

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/519, 31/4745; C07D 498/02, 491/02
US CL : 514/260.1, 265.1, 300, 301, 302
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/260.1, 265.1, 300, 301, 302

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US2003/0207900A1 (CHEN et al) 06 November 2003 (06.11.2003), see abstract.	1-12

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
09 July 2005 (09.07.2005)

Date of mailing of the international search report
28 SEP 2005

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Vickie Kim
Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/15118

Continuation of B. FIELDS SEARCHED Item 3:
REGISTRY, CAPLUS, USPATFUL, WEST
structure searched and term searched: psoriasis, differentiation , keratinocyte, etc